

REMARKS

Status of the Claims

Claims 1-55, 59, 66-69, 72, 77, 79, 81-85, 91-95, 100-101, 103-107 and 110-120 have been cancelled. Claims 60, 62, 108 and 131 has been amended. Claims 133-140 are new. After amendment, claims 56-58, 60-65, 70, 71, 73-76, 78, 80, 86-90, 96-99, 102, 108, 109 and 121-140 are pending.

Amendment of the Specification

As requested in the Office Action, the first paragraph of the Description of the instant application has been replaced with a paragraph to update continuity data.

Amendment of the Claims

Claims 60 and 62 have been amended to make the language of the claims more clear. Amendment of claim 131 is at least supported at page 3 lines 14-page 4 line 5 of the specification and by original claims 106, 107, and 115-118. Amendment of claim 108 and new claims 133-140 are at least supported at page 3 line 9 to page 4 line 5, page 7 ll. 13-16, page 15 ll. 1-3 and ll. 6-21, and by Figures 10A, 10B, 11A, 11B, 13A, and 13B, Examples 6-9, and original claims 106, 107, and 115-118 of the specification.

Rejection of Claims 56-58, 60-65, 70, 71, 73-76, 78, 80, 86-90, 96-99, 102, 108, 109, and 121-132 on the Ground of Nonstatutory Obviousness-Type Double Patenting Over U.S. Patent No. 6,734,018

Applicants file a Terminal Disclaimer herewith to overcome the rejection of claims 56-58, 60-65, 70, 71, 73-76, 78, 80, 86-90, 96-99, 102, 108, 109, and 121-132 on the ground of nonstatutory obviousness-type double patenting over U.S. Patent No. 6,734,018.

Rejection of Claim 62 under 35 U.S.C. §112, Second Paragraph

Claim 62 has been amended to remove language to an “extracting solution [that] is reactive with said anionic detergent.” It was asserted in the Office Action that language to this effect made the claim indefinite. While Applicants disagree with the assertion, the claim has

been amended to overcome this rejection in order to expedite further prosecution of the pending claims.

Rejection of Claims 56-58, 60-62, 64, 86-90, 96-99, 102, 108, 109, and 121-132 under 35

U.S.C. §103(a) as Being Unpatentable Over U.S. Patent No. 4,776,853

In the Office Action, it is alleged that U.S. Patent No. 4,776,853 ('853) teaches "the use of both hypotonic and hypertonic conditions as well as both nonionic and ionic detergents and nuclease treatment to hydrolyze both RNA and DNA," as in the present invention. It is acknowledged in the Office Action that the order in which tissue is exposed to such treatment conditions is different in the '853 patent compared to the pending claims, yet it is asserted that "the order of adding ingredients or treating agents is considered to be *prima facie* obvious." Applicants respectfully disagree with this assertion. The order of adding treatment agents determines what types of reactions/treatments occur and when they occur. Different orders of addition ultimately lead to the production of different products.

The claimed invention does not teach use of a nonionic detergent in a high salt solution as is disclosed in the '853 patent. In contrast, the claimed invention involves extracting a soft tissue sample with a hypotonic (low salt concentration) buffered extracting solution comprising a nonionic detergent. The use of a nonionic detergent in a high salt solution in the '853 patent is to "permit extraction of cytoplasmic components and soluble extracellular matrix components." Col. 3 ll. 42-43.

It is known in the art that the behavior of a nonionic detergent is greatly affected by salt concentration. Cloud point, critical micelle concentration, aggregation number, and hydration of micelles of nonionic detergents are all influenced by salt concentration. (See attached, Eur. J. Biochem. Vol. 276, pp. 6339-6345 (2000); J. of Colloid and Interface Science, Vol. 189, No. 1, pp. 117-122 (1997); <http://psyche.uthct.edu/shaun/SBlack/detergnt.html>; <http://pubs.acs.org/cgi-bin/abstract.cgi/langd5/1996/12/i14/abs/la951088a.html>). The efficiency of solubilizing proteins and other cellular components by a nonionic detergent is affected by salt concentration, and thus the detergent treatment step of the claimed invention (with hypotonic detergent solution) and that disclosed by the '853 patent (high salt detergent solution) are different and detergent-treated tissue produced by each is different.

The claimed invention does not teach lysis of cells with hypotonic buffer, followed by treatment with high salt solution containing nonionic detergent as in the '853 patent. The claimed invention also does not employ a hypotonic buffer and a high salt solution that both comprise protease inhibitors (i.e., EDTA) as is disclosed by the '853 patent.

In the claimed invention a soft tissue is extracted with a hypotonic buffered extracting solution comprising at least one nonionic detergent and at least one endonuclease. It is known in the art that hypotonic solutions have a lesser osmotic pressure than the fluid within tissue cells, and they cause a net flow of water across the semipermeable cell membrane into cells that are bathed in the solution. Water flows into a cell causing it to swell, and if the difference in osmotic pressure between the solution and the cytoplasm is significant enough, it will swell the cell until it bursts (e.g., lyses). Thus, in the claimed invention, the cells in the soft tissue can be lysed, exposing DNA and RNA molecules to digestion by the endonuclease in the extracting solution. Treatment with the extracting solution in the claimed invention enables cell lysis and nucleic acid digestion to be performed in a single step. In contrast, the '853 patent teaches away from lysis and digestion of DNA and RNA in a single step.

The '853 patent teaches lysis of cells with hypotonic buffer, followed by treatment with high salt solution containing nonionic detergent. The hypotonic buffer and the high salt solution both comprise protease inhibitors (i.e., EDTA). Following treatment with the high salt solution, the tissue has to be washed with distilled water and equilibrated with a buffered saline solution before treatment with nucleases. This is because the nucleases are not active at the high salt concentrations taught by the '853 patent (e.g., 1-2 M salt) or in the presence of certain protease inhibitors, like EDTA. Thus, great care has to be taken in washing and equilibrating tissue treated with high salt solutions as taught by the '853 patent before addition of nucleases.

In fact, the '853 patent teaches away from adding nucleases to the hypotonic buffer. The '853 patent discloses that its hypotonic buffer comprises a protease inhibitor, such as EGTA or EDTA, and that EDTA is a preferred protease inhibitor. EDTA and EGTA are metal chelators that strongly inhibit or prevent endonuclease activity in the hypotonic buffer. (It is well known in the art that endonucleases (i.e., DNase, RNase, and restriction enzymes) are inhibited by metal chelators (i.e., EDTA), anionic detergents (i.e., SDS), and high salt concentrations.) (See

attached, <http://www.neb.com/nebecomm/products/faqCategory1.asp>; Benzonase endonuclease marketing materials from Merck; <http://www.ambion.com/techlib/tips/dnase1demystified.html>.)

Despite the assertion in the office action that the order of addition of certain ingredients is obvious, clearly the order of steps used to treat a tissue in the claimed invention is relevant, and using different combinations of ingredients will have different results. In view of this analysis, Applicants respectfully request the withdrawal of the rejection of claims 56-58, 60-62, 64, 86-90, 96-99, 102, 108, 109, and 121-132 as obvious over the '853 patent.

Rejection of Claim 63 under 35 U.S.C. §103(a) as Being Unpatentable Over U.S. Patent No. 4,776,853 in View of U.S. Patent No. 5,531,791

U.S. Patent No. 5,531,791 ('791) does not teach a process for decellularization of soft tissue. In view of the discussion above, the '791 and '853 patents taken alone or together do not teach decellularization of soft tissue as in the claimed invention. Applicants respectfully request withdrawal of the rejection of claim 63.

Rejection of Claim 65 under 35 U.S.C. §103(a) as Being Unpatentable Over U.S. Patent No. 4,776,853 in View of U.S. Patent No. 5,357,636

U.S. Patent No. 5,357,636 ('636) does not teach a process for decellularization of soft tissue.

The decontaminating agents taught by the '636 patent are enclosed between the inside and outside layers of a medical glove. If the glove is punctured, the decontaminating agent is released to protect the wearer, both by coating the object that punctured the glove and by transfer to the area of the hand that may have been injured by the puncturing object. The '636 patent does not teach using decontaminating agents to store a soft tissue as in the claimed invention.

In view of the discussion above, the '636 and '853 patents taken alone or together do not teach decellularization of soft tissue as in the claimed invention.

Rejection of Claims 70, 71, 73-75, and 86 under 35 U.S.C. §103(a) as Being Unpatentable Over
U.S. Patent No. 4,776,853 in View of Moreno, *et al.*

Moreno, *et al.* do not teach a process for decellularization of soft tissue. In view of the discussion above, Moreno, *et al.* and the '853 patent taken alone or together do not teach decellularization of soft tissue as in the claimed invention. Applicants respectfully request withdrawal of the rejection of claims 70, 71, 73-75, and 86.

Rejection of Claims 76, 78, and 80 under 35 U.S.C. §103(a) as Being Unpatentable Over U.S.
Patent No. 4,776,853 in View of U.S. Patent No. 5,095,925

U.S. Patent No. 5,095,925 ('925) does not teach a process for decellularization of soft tissue. In view of the discussion above, the '925 and '853 patents taken alone or together do not teach decellularization of soft tissue as in the claimed invention. Applicants respectfully request withdrawal of the rejection of claims 76, 78, and 80.

Copending Applications

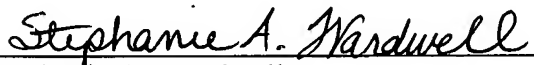
In the Office Action, it was requested that Applicants provide a list of copending applications setting forth similar subject matter to the pending claims and a copy of such copending claims. U.S. Application No. 10/694,190, filed October 28, 2033, is directed to a "Process for Devitalizing Soft-Tissue Engineered Medical Implants, and Devitalized Soft-Tissue Medical Implants Produced," and the inventors are, Lloyd Wolfinbarger Jr., Perry Lange, Alyce Linthurst, Eric Moore, and Barry Nolf. Claims pending in this application are submitted herewith.

Conclusion

In view of the foregoing, the application is respectfully submitted to be in condition for allowance, and prompt favorable action thereon is earnestly solicited. If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

To effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response; please charge any deficiency in fees or credit any overpayments to Deposit Account No. 50-1881 (95176562-004002).

Respectfully submitted,
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